(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/72825 A1

(51) International Patent Classification[7]: A61K 9/14, 9/48, 47/32, 47/38, A61P 3/04

(21) International Application Number: PCT/US00/14106

(22) International Filing Date: 23 May 2000 (23.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/320,188 29 May 1999 (29.05.1999) US

(71) Applicant: ABBOTT LABORATORIES [US/US]; D377/AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

(72) Inventors: LAW, Devalina; 835C Country Club Drive, Libertyville, IL 60048 (US). KRILL, Steven, L.; 44 Meyersville Road, Chatham, NJ 07928 (US). SCHMITT, Eric, A.; 319 Evergreen Court, Libertyville, IL 60048 (US). FORT, James, J.; 2700 Leafield Terrace, Midlothian, VA 23113 (US).

(74) Agents: SICKERT, Dugal, S. et al.; D377/AP6D, 100 Abbott Park Road, Abbott Park, IL 60064-6050 (US).

(81) Designated States *(national)*: CA, JP, MX.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/72825 A1

(54) Title: NOVEL FORMULATIONS COMPRISING LIPID-REGULATING AGENTS

(57) Abstract: The present invention is directed to a solid formulation comprising the lipid-regulating agent dispersed in a hydrophilic, amorphous polymer in which said lipid-regulating agent is present as a meta-stable, amorphous phase.

Novel Formulations Comprising Lipid-Regulating Agents

Field of the Invention

The present invention relates to novel formulations comprising lipid-regulating agents.

Background of the Invention

2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethylester, also known as fenofibrate, is representative of a broad class of compounds having pharmaceutical utility as lipid regulating agents. More specifically, this compound is part of a lipid-regulating agent class of compounds commonly known as fibrates, and is disclosed in U.S. Patent No. 4,058,552.

Fenofibrate has been prepared in several different formulations, c.f., U.S. Patent No. 4,800,079 and U.S. Patent No. 4,895,726. U.S. Patent No. 4,895,726 discloses a co-micronized formulation of fenofibrate and a solid surfactant.

U.S. Patent No. 4,961,890 discloses a process for preparing a controlled release formulation containing fenofibrate in an intermediate layer in the form of crystalline microparticles included within pores of an inert matrix. The formulation is prepared by a process involving the sequential steps of dampening said inert core with a solution based on said binder, then projecting said fenofibrate microparticles in a single layer onto said dampened core, and thereafter drying, before said solution based on said binder dissolves said fenofibrate microparticles, and repeating said three steps in sequence until said intermediate layer is formed.

European Patent Application No. EP0793958A2 discloses a process for producing a fenofibrate solid dosage form utilizing fenofibrate, a surface active agent and polyvinyl pyrrolidone in which the fenofibrate particles are mixed with a polyvinyl pyrrolidone solution. The thus obtained mixture is granulated with an aqueous solution of one or more surface active agents, and the granules thus produced are dried.

PCT Publication No. WO 82/01649 discloses a fenofibrate formulation having granules that are comprised of a neutral core that is a mixture of saccharose and starch. The neutral core is covered with a first layer of fenofibrate, admixed with an excipient and with a second microporous outer layer of an edible polymer.

U.S. Patent No. 5,645,856 describes the use of a carrier for hydrophobic drugs, including fenofibrate, and pharmaceutical compositions based thereon. The carrier comprises a digestible oil and a pharmaceutically-acceptable surfactant component for dispersing the oil in vivo upon administration of the carrier, which comprises a hydrophilic surfactant, said surfactant component being such as not to substantially inhibit the in vivo lipolysis of the digestible oil.

Sheu, M. T., et al, *Int. J. Pharm.* 103 (1994) 137-146, reported that a dispersion of fenofibrate in PVP still maintains the same crystalline form of the drug itself.

Palmieri, G. F., et al, *Pharma Sciences* 6 (1996) 188-194, reported that a dispersion of crystalline fenofibrate could be prepared in PEG 4000. The authors concluded solid solutions in PEG are formed when the amount of fenofibrate is less than 15% and the dissolution rate is increased, particularly for the 90/10 carrier/drug ratio.

Gemfibrozil is another member of the fibrate class of lipid-regulating agents. U.S. Patent No. 4,927,639 discloses a disintegratable formulation of gemfibrozil providing both immediate and sustained release, comprising a tablet compressed from a mixture of a first and second granulation, and a disintegration excipient operable to effect partial or complete disintegration in the stomach. The first granulation comprises finely divided particles of pure gemfibrozil granulated with at least one cellulose derivative, and the second granulation comprises finely divided particles of pure gemfibrozil granulated with a pharmaceutically-acceptable water soluble or insoluble polymer which are then uniformly coated with a pharmaceutically-acceptable (meth)acrylate copolymer prior to admixture with the first granulation. The first and second granulations are present in the final composition in a ratio of from about 10:1 to about 1:10.

U.S. Patent 4,925,676 discloses a disintegratable gemfibrozil tablet providing both immediate and enteric release, which is compressed from a mixture of a first granulation of gemfibrozil with at least one acid-disintegratable binder, and a second granulation formed from the first granulation, but regranulated or coated with an alkali-disintegratable formulation of at least one substantially alkali-soluble and substantially acid-insoluble polymer.

Another class of lipid-regulating agents are commonly known as statins, of which pravastatin and atorvastatin are members. U.S. Patents 5,030,447 and 5,180,589 describe stable pharmaceutical compositions, which when dispersed in water have a pH of at least 9, and include a medicament which is sensitive to a low pH environment, such as prevastatin, one or more fillers such as lactose and/or microcrystalline cellulose, one or more binders, such as

microcrystalline cellulose (dry binder) or polyvinylpyrrolidone (wet binder), one or more disintegrating agents such as croscarmellose sodium, one or more lubricants such as magnesium stearate and one or more basifying agents such as magnesium oxide.

It is an object of the present invention to provide formulations of lipid-regulating agents having enhanced bioavailability when compared to commercially available formulations.

Summary of the Invention

The present invention is directed to a solid formulation comprising the lipid-regulating agent dispersed in a hydrophilic, amorphous polymer in which said lipid-regulating agent is present as a metastable, amorphous phase. The size reduction obtained through the preparation of a dispersion is usually difficult to obtain. However, by using any technique that results in the dispersion of the lipid-regulating agent in an amorphous polymer, such as, for example, solvent evaporation or fusion, results in an increase in the dissolution rate and oral bioavailability of the said lipid-regulating agent.

The formulation may be administered directly, diluted into an appropriate vehicle for administration, encapsulated into hard gelatin shells or capsules, or compressed into tablets, for administration, or administered by other means obvious to those skilled in the art.

Brief Description of the Drawings

Figure 1 is a graph showing the plasma concentration in fed dogs of the formulation of Example 1 and a reference compound.

Detailed Description of the Invention

The bulk lipid-regulating agent may be prepared by any available method, as for example the compound fenofibrate may be prepared by the procedure disclosed in U.S. Patent No. 4,058,552, or the procedure disclosed in U.S. Patent No. 4,739,101, both herein incorporated by reference.

The composition comprising the lipid-regulating agent is prepared by dissolving or dispersing the lipid-regulating agent and hydrophilic, amorphous polymer in a sufficient amount of solvent. The solvent is evaporated to yield a solid mass which is ground, sized and optionally formulated into an appropriate delivery system. Other techniques, known in the art, such as for example fusion or fusion-evaporation, may also be used.

The delivery system of the present invention results in increased solubility and bioavailability, and improved dissolution rate of the lipid-regulating agent.

If the solvent evaporation technique is used, suitable solvents include, for example, lower alkyl alcohols such as methanol, ethanol, or any other pharmaceutically-acceptable organic solvent in which the lipid-regulating agent and the polymers have appreciable solubility.

Suitable hydrophilic, amorphous polymers include, for example, polyvinylpyrrolidone (PVP),

hydroxypropylmethylcellulose (HPMC), or other pharmaceutically-acceptable hydrophilic, amorphous polymers such as for example, Eudragits®.

Other pharmaceutically-acceptable excipients may be added to the formulation prior to forming the desired final product. Suitable excipients include, for example, lactose, starch, magnesium stearate, or other pharmaceutically-acceptable fillers, diluents, lubricants, disintegrants, etc., that might be needed to prepare a capsule or tablet.

The resulting composition comprising the lipid-regulating agent may be dosed directly for oral administration, diluted into an appropriate vehicle for oral administration, filled into capsules, or made into tablets for oral administration, or delivered by some other means obvious to those skilled in the art. The said composition can be used to improve the oral bioavailability and solubility of said lipid-regulating agent.

The invention will be understood more clearly from the following non-limiting representative examples:

Example 1

A mixture (3 g) of fenofibrate and PVP (PF 17) in a ratio of 15:85 was dissolved in 4.5 mL of ethanol. The ethanol was evaporated under vacuum at 85°C. The resulting dry solid was then ground and sized through a 60-100 mesh screen. 446.7 mg of the granular formulation (containing 67 mg fenofibrate) was filled into individual capsules.

Example 2

A mixture (3 g) of statin and PVP (PF 17) in a ratio of 15:85 is dissolved in sufficient ethanol. The ethanol is

evaporated under vacuum at 85°C. The resulting dry solid is then ground and sized through a 60-100 mesh screen. The solid is then filled in capsules to obtain the desired unit dose.

Example 3

Capsules prepared by the process described in Example 1, and from a commercial fenofibrate composition, Lipanthyl 67M (Groupe Fournier) (Reference), were administered to a group of dogs at a dose of 67 mg fenofibrate/dog. The plasma concentrations of fenofibric acid were determined by HPLC. Concentrations were normalized to a 6.7 mg/kg dose in each dog. Figure 1 presents the resulting data in graph form. The results provided as mean ± SD, n=6, were as follows:

Lipanthyl 67M (Reference):
Cmax = 4.06 ± 0.53 mcg/ml
Tmax = 1.0 ± 0.0 hr
$t_{1/2}$ = 9.5 hr
AUC (0-24) = 21.37 ± 2.56 mcg•hr/ml

Capsule of Example 1:
Cmax = 2.22 ± 0.31 mcg/ml
Tmax = 2.3 ± 1.2
$t_{1/2}$ = 7.7 hr
AUC (0-24) =18.04 mcg•hr/ml
AUC relative to reference = 84.4%

Claims

1. A composition comprising a lipid-regulating agent dissolved or dispersed in a hydrophilic, amorphous polymer in which said lipid-regulating agent is present as a meta-stable, amorphous phase.

2. A composition of claim 1 wherein said lipid-regulating agent is a fibrate.

3. A composition of claim 2 wherein said fibrate is fenofibrate.

4. A composition of claim 1 wherein said lipid-regulating agent is a statin.

5. A composition of claim 4 wherein said statin is prevastatin.

6. A composition of claim 4 wherein said statin is atorvastatin.

7. A composition of claim 1 further comprising dissolving the lipid-regulating agent into a hydrophilic, amorphous polymer in a sufficient amount of solvent, then removing said solvent to yield a solid composition comprising said lipid-regulating agent in a stable, amorphous phase.

8. A composition of claim 7 wherein at least one or more of said solvents is selected from lower alkyl alcohol such as for example, methanol, ethanol, or any other pharmaceutically-acceptable organic solvent in which the lipid-regulating agent and the polymer have appreciable solubility.

9. A composition of claim 8 wherein one or more of said solvents is ethanol.

10. A composition of claim 1 wherein at least one or more of said hydrophilic polymers is selected from polyvinylpyrrolidone (PVP), hydroxypropylmethylcellulose (HPMC), or other pharmaceutically-acceptable hydrophilic, amorphous polymers such as for example, Eudragits®.

11. A composition of claim 10 wherein at least one or more of said hydrophilic polymers is polyvinylpyrrolidone.

12. A delivery system comprising a composition of claim 1.

13. A delivery system of claim 12 wherein said delivery system is a capsule or tablet.

14. A method of treating hyperlipidemia comprising the administration of a composition of claim 1 to a patient.

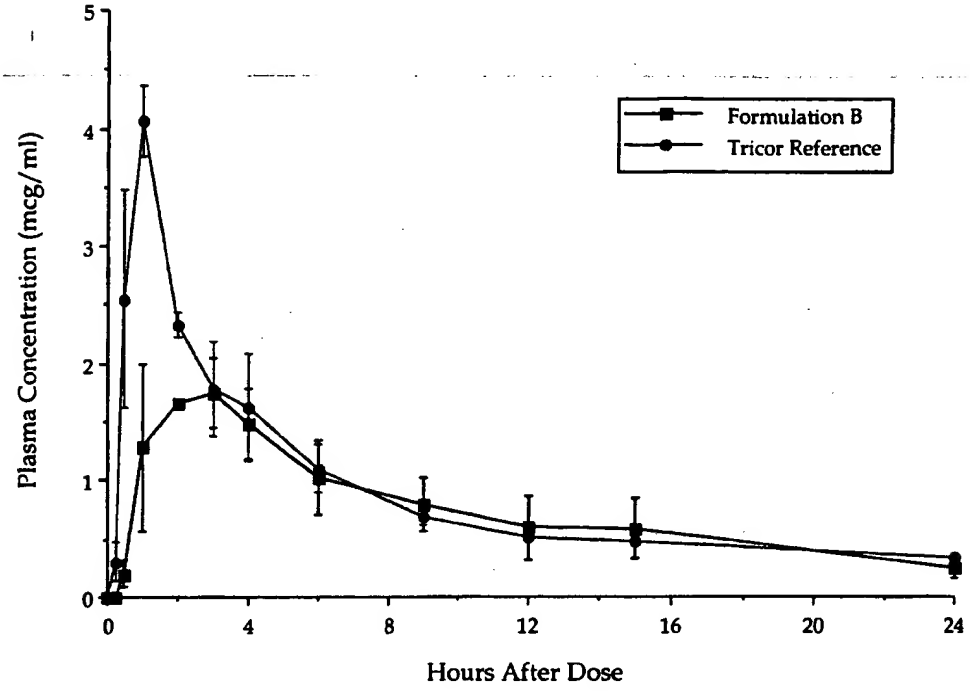
15. A method of treating hyperlipidemia comprising the administration of a composition of claim 3 to a patient.

16. A method of treating hyperlipidemia comprising the administration of a composition of claim 13 to a patient.

FIG. 1

Insert dog data

Mean (±SEM, n=3) Plasma Concentrations of Fenofibric Acid after a 67 mg Oral Dose of Fenofibrate in Non-fasted Dogs



INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 00/14106

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/14 A61K9/48 A61K47/32 A61K47/38 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 36318 A (LEK TOVARNA FARMACEVTSKIH ;REBIC LJUBOMIRA BARBARA (SI); KERC JANE) 21 November 1996 (1996-11-21) page 4, paragraph 2 page 5, last paragraph -page 6, paragraph 2 page 10, paragraph 3 claims 2,7 ---	1-3,7-16
X	EP 0 462 066 A (WARNER LAMBERT CO) 18 December 1991 (1991-12-18) page 2, line 28 -page 3, line 7; claims; example 1 --- -/--	1,2, 10-16

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 September 2000	12/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 00/14106

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 31361 A (FOURNIER LAB SA) 23 July 1998 (1998-07-23) page 5, line 22 - last line page 6, line 21 -page 7, line 7 page 10, line 26 -page 11, line 3; claims 1-3,13,14; example 1	1-3,7-13
X	MORRIS K A ET AL: "Characterization of humidity-dependent changes in crystal properties of a new HMG-CoA reductase inhibitor in support of its dosage form development." INTERNATIONAL JOURNAL OF PHARMACEUTICS (AMSTERDAM), vol. 108, no. 3, 1994, pages 195-206, XP000929694 ISSN: 0378-5173 page 196, column 1, paragraph 3 page 197, column 2, last paragraph -page 198, column 1, paragraph 1 page 201, column 1, last paragraph -column 2, line 1 page 204, column 2, paragraph 2	1,7,12, 13
X	WO 98 15264 A (LOEFROTH JAN ERIK ;ASTRA AB (SE); OEDMAN JONAS (SE)) 16 April 1998 (1998-04-16) page 7, line 9 -page 9, line 8 page 9, line 22 - line 26; claims 1-6,9,10,12; example 5	1,4,7-16

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-16 relate to a compound defined by reference to a desirable characteristic or property, namely a "lipid-regulating agent". The term "lipid-regulating agent" as used in the present independent claims 1, 12, 14-15 and in dependent claims 2-11, and 13 defines the active agent by its pharmacological effect. However, a compound canot be sufficiently characterised by its pharmacological effect as it is done by an expression like "lipid-regulating agent", because it is impossible to know which substances are encompassed in this expression. Moreover, a compound cannot be sufficiently characterised by the term "regulating", because this term has no well-recognised meaning and is therefore unclear.

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for the concept of "lipid-regulating agent" and those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds mentioned in claims 2-6.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/US 00/14106

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9636318 A	21-11-1996	SI 9500173 A	31-12-1996
		AU 698360 B	29-10-1998
		AU 5710396 A	29-11-1996
		CZ 9703655 A	15-04-1998
		EP 0827397 A	11-03-1998
		HU 9901457 A	30-08-1999
		JP 11505542 T	21-05-1999
		PL 323487 A	30-03-1998
		SK 153497 A	08-04-1998
		US 6042847 A	28-03-2000
EP 0462066 A	18-12-1991	AU 7837891 A	19-12-1991
		CA 2044509 A	16-12-1991
		FI 912883 A	16-12-1991
		JP 4230215 A	19-08-1992
		NO 912303 A	16-12-1991
		PT 97988 A	31-03-1992
		ZA 9104586 A	29-04-1992
WO 9831361 A	23-07-1998	FR 2758459 A	24-07-1998
		AU 5336798 A	07-08-1998
		BR 9806738 A	29-02-2000
		CA 2219475 A	17-07-1998
		CZ 9902535 A	17-11-1999
		EP 0952829 A	03-11-1999
		NO 993519 A	16-09-1999
		PL 334748 A	13-03-2000
		US 6074670 A	13-06-2000
		ZA 9800324 A	12-08-1998
WO 9815264 A	16-04-1998	AU 4578097 A	05-05-1998
		EP 0948320 A	13-10-1999